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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/578,900	05/26/2000	John P. Carulli	032796-019	8399

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/578,900	CARULLI ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-61* is/are pending in the application.

4a) Of the above claim(s) *3-5 and 8-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,7 and 48-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Applicati n Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *2/3/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Action is in response to the communication filed on 8/25/03. The amendment to the specification has been entered. Claim 6 has been amended. Claims 1-61 are pending in the application in the application and are addressed herein.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Election/Restrictions

3. For the reasons previously set forth, claims 3-5 and 8-47 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the communication filed 3/22/02.

4. Claims 1, 2, 6, 7 and 48-61 are examined herein.

5. Applicants are respectfully reminded that this application contains claims 3-5 and 8-47 drawn to an invention nonelected with traverse in the communication filed 3/22/02. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Priority

6. As set forth in the previous Office Action, Applicant's claim for domestic priority under 35 U.S.C. 119(e) and 120 and/or 121 is acknowledged. However, the provisional applications upon which priority is claimed (60/071449 and 60/105511) fail to provide adequate support under 35 U.S.C. 112 for claims 1, 2, 6 and 7 of this application. The provisional applications do not disclose the sequences of Zmax1, HBM, or the polymorphisms of Zmax1/HBM (i.e. the polymorphisms of Table 4) encompassed by the claims.

Sequence Rules

The objection to the specification for not complying with the sequence rules has been withdrawn in view of the amendment to the specification adding appropriate sequence identifiers (SEQ ID NOS.) and submitting a proper paper sequence listing and disk (CRF).

Claim Rejections - 35 USC § 101 and 112

7. Claims 1, 2, 6, 7 and 48-61 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well-established utility, for the reasons of record.

8. Additionally, claims 1, 2, 6, 7 and 42-61 also remain rejected under 35 U.S.C. 112, first paragraph, for the reasons of record. Specifically, since the claimed invention is not supported by either a substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

9. The Examiner would like to thank the Applicants for pointing out the typographical error indicating that claims 42-47 were rejected under 35 USC 101 and 112. As Applicants pointed

out, claims 42-47 had been withdrawn from further consideration. Therefore, claims 42-47 are not rejected. Claims 42-47 are, in fact, withdrawn from consideration for the reasons of record.

Response to Arguments

10. Applicant's arguments filed 8/25/03 have been fully considered but they are not persuasive.

11. The instant claims are drawn to a method for identifying a molecule involved in lipid regulation comprising identifying a molecule that binds to, or that inhibits the binding of a molecule to, HBM or Zmax1 (see claim 1); as well as a method for identification of candidate molecules involved in lipid regulation by identifying molecules that bind to the nucleic acid of Zmax1 (SEQ ID NO: 1), or a polymorphism of Table 4 except one specific polymorphism, or an HBM nucleic acid having SEQ ID NO: 2 (see claim 6).

It is noted that the Applicants are correct in their understanding that the rejection of the claims (which are drawn to methods of identifying molecules involved in lipid regulation) is based on the credibility of the asserted utilities for Zmax1 and HBM (a polymorphism of Zmax1), namely that Zmax1 and HBM are involved in lipid regulation (see paragraph bridging pages 11-12 of the response filed 8/25/03, hereafter referred to as "the response"). Since the Zmax1 and HBM molecules are not supported by a specific, credible or well-established utility, then any methods using the Zmax1 or HBM molecules would also not be supported by a specific, credible or well established utility.

Applicants argue that contrary to the allegations in the Office Action, the involvement of HBM and Zmax1 in lipid regulation is clearly disclosed in the application. Applicants specifically point to pages 10-11, and Example 3 at pages 125-128.

It is noted the specification on page 10 (lines 13-21) indicates,

> "The present invention identifies the Zmaxl gene and the HBM gene, which can be used to determine if people are predisposed to abnormal lipid levels and, therefore, susceptible to diseases mediated by lipids, including, for example, atherosclerosis, arteriosclerosis and associated conditions. Individuals with the HBM gene have lower LDL, triglyceride and VLDL levels and higher HDL levels. In other words, the HBM gene is a suppressor of atherosclerosis, arteriosclerosis and associated conditions. This in vivo observation is a strong evidence that treatment of normal individuals with the HBM gene or protein, or fragments thereof, will ameliorate atherosclerosis, arteriosclerosis and conditions related thereto."

Here the specification indicates an observation that individuals with the HBM gene have lower LDL, triglyceride and VLDL levels and higher HDL levels. Based on this mere observation, Applicants conclude that, "the HBM gene is a suppressor of atherosclerosis, arteriosclerosis and associated conditions". Applicants do not offer any scientific data to support their allegation that the HBM gene is a suppressor of atherosclerosis or arteriosclerosis. Data which would support the allegation that HBM is a atherosclerosis/arteriosclerosis suppressor would include, for example, data indicating that when HBM is administered to a animal having atherosclerosis or arteriosclerosis, the treated animal shows a reduction in atherosclerosis/arteriosclerosis.

Example 3 in the specification discloses,

> "Since Zmaxl has similarity to the LDL receptor family of genes, it may be involved in lipid metabolism. However, others have reported that lipid profile variables did not show significant association with bone mass and could not be used as indicators for bone mineral density (Zabaglia et al., "An exploratory study of association between lipid profile and bone mineral density in menopausal women in a Campinas reference hospital," Cad. Saude Publica 14: 779-86 (1998)). Zmaxl may be normally involved in regulating bone density by depositing calcium during bone remodeling." (See paragraph bridging p. 125-126 of the specification); and,

> "To test whether the HBM gene was involved in lipid regulation, biochemical tests were performed to measure serum level of various lipid containing molecules or precursors in affected and unaffected HBM family members to test whether the HBM mutation in the

> Zmax1 gene effects lipid metabolism... The results obtained were statistically significant: (1) Triglyceride levels were generally lower in affected individuals than in unaffected individuals, and (2) very low density lipoprotein (VLDL) levels were generally lower in affected individuals than in unaffected individuals. Additionally, the following comparisons approached statistical significance (p=0.06): (1) high density lipoprotein (HDL) levels were higher in affected males than in unaffected males, and (2) the ratio of low density lipoprotein (LDL) to high density lipoprotein (HDL) was generally higher in affected males than in unaffected males." (See p. 126, lines 4-27).

Here, Applicants indicate the Zmax1 has "similarity" to the LDL receptor family of genes, but it is not clear exactly how similar Zmax1 is to the LDL receptors. Applicants acknowledge that the prior art had not made a connection between lipid metabolism and bone mineral density. In this Example, Applicants try to associate the HBM gene with lipid metabolism by evaluating the serum levels of some lipid containing molecules in individuals with and without HBM. The only statistically significant data disclosed indicates the individuals having the HBM polymorphism also have generally lower triglycerides levels and generally lower VLDL levels compared to individuals without HBM.

Applicants point to the passages recited above (p.10-11 and 125-128 of the specification) to indicate a correlation between Zmax1 (as well as its polymorphism HBM) and lipid regulation. However, as mentioned above, Applicants have only indicated that individuals having HBM also have lower serum levels of triglycerides and VLDL. It is respectfully pointed out that there is absolutely no biochemical data indicating any association of Zmax1 to lipid regulation.

Regarding the alleged association of HBM to lipid regulation, it was pointed out in the previous Office Action that serum lipid levels can be affected by a number of different factors including diet (see previous Office Action, page 6) as well as genetic elements. However, the

specification does not indicate that the difference in serum lipid levels between the HBM individuals and non-HBM individuals is due exclusively to HBM and not some other factor, such as diet.

Applicants also argue that Zmax1 protein has "has a degree of sequence homology and feature in common with the LDL receptor" (see p. 13 of the response), and refers to pages 83-84 of the specification. Furthermore Applicants state, "While the noted relationship between Zmax1 and the LDL receptor, standing alone, would not be sufficient to establish whether Zmax1 is involved in lipid regulation, this observation supports the credibility of the conclusions indicated by the experimental results." (p. 13 of response)

In reply it is respectfully pointed out that the specification does not disclose the exact degree of sequence homology between Zmax1 and the LDL receptor. Therefore, it is unclear exactly how similar the two molecules are. Regardless of the level of similarity between Zmax1 and the LDL receptor it is pointed out that the LDL receptor is not solely involved in lipid metabolism (see p. 6-7 of the previous Office Action). Since the LDL receptor is known to be involved in processes other than lipid metabolism (as indicated in the cited art), one of ordinary skill in the art would not be able to associate Zmax1 with LDL regulation based solely on sequence similarity. Since the LDL receptor is involved in other processes, it is possible that Zmax1 is also involved one of the processes other than lipid regulation. Therefore, the Examiner disagrees with Applicants' allegation that the sequence similarity of Zmax1 to the LDL receptor supports the credibility of the conclusion that Zmax1 is involved in lipid regulation.

The Applicants also argue that Zmax1 binds to ApoE, which was known to be involved in lipid regulation (see p. 14 of the response). However, page 115 of the specification, merely

indicates that Zmax1 and HBM "interact with several proteins such as ApoE". There is no biochemical data provided which indicates how Zmax1 or HBM "interacts" with ApoE. The specification does not disclose if the "interaction" has been demonstrated in vitro or in vivo, if the interaction is a direct or indirect interaction, or even if it is a specific interaction. Therefore, it is not clear if Zmax1 and HBM functionally interact with ApoE or if it merely a non-specific interaction that would not affect the function of any of the molecules (i.e. Zmax1, HBM, or ApoE). Without a clear indication of how Zmax1 and HBM "interact" with ApoE one of ordinary skill in the art could use this information to conclude that Zmax1 or HBM were involved in lipid regulation.

The Applicants also cite Zabaglia as a reference that attempts to correlate lipid regulation and bone mineral density (BMD). It is pointed out that Zabaglia concludes, "The conclusions were that lipid profile variables did not show a significant association with bone mass and could not be used as indicators for bone mineral density." (See last sentence of the abstract). The Applicants acknowledge this statement by Zabaglia and argues that it does not contradict their assertion (see p. 14 or the response, last paragraph). The Examiner respectfully disagrees with the Applicants. The purpose of Zabaglia was to look for a correlation between lipid regulation and bone mass (or BMD); however, Zabaglia could not make such a correlation. Therefore, Zabaglia does not support Applicants position and in fact casts doubt onto the notion that a relationship exists between lipid regulation and bone mass.

Applicants also argue that the credibility of the asserted utility has been born out in reports in the literature. It is pointed out that the Applicants have cited references which were published after the filing of the instant application. Although the Applicants indicate that the

cited references refers to prior art, the Applicants have not explicitly indicated the prior art by author, title and date nor have Applicants supplied copies of the prior art references which the cited post filing art refers to. It is respectfully pointed out that the asserted utility must evident in the specification or the prior art (not the post filing art). Therefore, applicants' arguments regarding the post filing art cannot be fully considered until the prior art that Applicants wish to be considered is supplied. The Examiner will consider any properly filed prior art supplied by the Applicants.

The Applicant also argue that since it is the difference between the presence or absence of the HBM variant or Zmax1 that has been shown to correspond to an altered lipid profile by the in vivo data presented in the application, the link between Zmax1 and lipid regulation has also been credibly established. The Examiner respectfully disagrees that data presented in the application establishes a correlation between either Zmax1 or the HBM variant and lipid regulation for the reasons indicated herein. Therefore, the asserted utility for Zmax1 (and HBM) is not a credible utility.

The Applicants also argue the references cited in the prior Office Action do not provide a reason to doubt the asserted utility (see pages 16-17 of the response). Regarding the Ye reference, applicants argue that the reference does not in any way cast doubt on the utility of the invention. In response, it is respectfully pointed out that Ye indicates that there are a number of different factors that can effect lipid regulation in an animal. Included in the factors that may be involved in lipid regulation (as indicated by Ye) is diet as well genetic polymorphisms. As indicated above, however, the instant application does not take into consideration that the difference in lipid regulation between Zmax1 and HBM individuals may be due to other factors

such as diet. There is no indication the results disclosed in the specification were not due to any of these other factors including diet or other genetic polymorphisms. Furthermore, regarding genetic polymorphisms with respect to lipid metabolism, Ye teaches (as indicated in the previous Office Action),

> "Although more and more data are available on the effects of genetic polymorphisms in genes related to lipid metabolism and the responsiveness to dietary fat and cholesterol, no consistent effects of most reported genetic factors have been seen. The major problems related to these discrepancies are sample size, effects of age and sex, different ethnic and cultural (dietary) backgrounds of the participants, different dietary protocols used, and the difficulty of insuring compliance. More clinical trials in large populations with standardized protocols are needed to study further the effects of these polymorphisms on the responsiveness to dietary fat and cholesterol." (See p. 1282S, first column).

Thus Ye teaches that although polymorphisms in genes involved in lipid regulation may exist, the effects of these polymorphisms on lipid regulation varies greatly between groups of people, based on a number of different factors, including diet as well as age, sex and ethnic background.

Regarding the Willnow reference, Applicants argue that Willnow teaches that the LDL receptor family of proteins have many varied functions, but provides no reason to doubt the credibility of the asserted utility. In response, it is acknowledged that Willnow does teach that LDL receptors have many varied functions, including non-lipid regulating functions. It is respectfully pointed out that the instant application attempts to make a correlation between Zmax1 as well as HBM and lipid regulation based upon (among other things) sequence homology. However, if LDL receptors have non-lipid regulation functions then one of ordinary skill in the art would not be able to make a credible assertion that Zmax1 and HBM must also

have lipid-regulating functions. It is possible that Zmax1 and HBM have different (non-lipid regulating) functions.

Finally applicants argue that identification of molecules that bind to a protein involved in lipid regulation is a well-established utility. It is acknowledged that methods of identifying molecules that bind to a protein known to be involved in lipid regulation have utility as long as the proteins have been shown to be involved in lipid regulation. However, for the reasons of record and herein, in the instant case the specification has not established the Zmax1 or HBM actually are involved in lipid regulation. If sufficient evidence were presented to show that Zmax1 and HBM were known to be involved in lipid regulation at the time the application was filed, then the method of identifying molecules that bind to a protein involved in lipid regulation would have credible utility.

Regarding the rejection of claims under 35 USC 112, first paragraph in view of the 101 rejection, Applicants argue that credible utility for Zmax1 and HBM have been established. The Examiner respectfully disagrees for the reasons stated herein.

Miscellaneous

The rejection of claims under 35 USC 112, second paragraph, and 35 USC 112, first paragraph (new matter) have been withdrawn in view of applicants persuasive arguments and/or claim amendments.

Conclusion

No claim is allowed.

3. This application contains claims drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

DAVID T. NGUYEN
PRIMARY EXAMINER

J. Eric Angell
AU 1635.